Trial Establishes Preferred Treatment for Some People With Esophageal Cancer

Chemo both before and after surgery—called perioperative chemotherapy—should be recommended for locally advanced esophageal cancer.

July 15, 2024 By National Cancer Institute

By Linda Wang

A large clinical trial looks to have settled a debate over how best to treat most people with locally advanced esophageal cancer, where the disease has spread just outside of the esophagus but not to other parts of the body.

Typically, these people get one of two treatments: chemotherapy followed by surgery and then more chemotherapy, or chemotherapy and radiation followed by surgery and no further treatment.

It's been unclear, however, if one approach was more effective than the other.

In the trial, people treated with chemotherapy both before and after surgery, which is known as perioperative chemotherapy, lived considerably longer than those who received chemotherapy and radiation before surgery, known as neoadjuvant treatment.

Based on the study's findings, perioperative chemotherapy should be the recommended approach for people with locally advanced esophageal cancer, said Jens Hoeppner, MD, of the University of Bielefeld in Germany, who led the study. Dr. Hoeppner presented the findings at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago on June 2.

"The results have been long awaited among those of us who treat esophageal cancer," said Karyn A. Goodman, MD, of the Icahn School of Medicine at Mount Sinai in New York, who discussed the results during the meeting but was not involved in the study.

Dr. Goodman also noted, however, that the treatment landscape for esophageal cancer is rapidly evolving. Although it's important to have some resolution to this particular debate, she said, newer treatments, including immunotherapies, are also now an option for people with locally advanced esophageal cancer.

In addition, researchers are also testing whether combining these regimens with other therapies can lead to even better outcomes for patients. In other words, she stressed, how locally advanced esophageal cancer is treated is going to continue to evolve in the coming years.

Two standard of care treatment options

In the United States, it is estimated that more than 22,000 people will be diagnosed with esophageal cancer this year. Approximately half of these cases will be diagnosed at a locally advanced stage.

Surgery was long the primary treatment for locally advanced esophageal cancer. That changed over the past two decades, with several large trials showing that the addition of perioperative chemotherapy or neoadjuvant chemotherapy plus radiation therapy improved how long people lived.

From those trials, two options emerged as the recommended treatments: a perioperative chemotherapy regimen called FLOT and a neoadjuvant chemotherapy and radiation regimen called CROSS (see box).

With two proven, highly effective treatment approaches available, Dr. Hoeppner and his colleagues decided to launch a trial to answer a question that arose frequently among oncologists: Which one is best for their patients?

One regimen rises above the other

In the new trial, dubbed ESOPEC and funded by the German Research Foundation, 438 people with locally advanced esophageal cancer were randomly assigned to receive either perioperative chemotherapy with the FLOT regimen or neoadjuvant chemoradiation with the CROSS regimen.

After completing treatment, 35 of the 191 patients in the FLOT group had complete disappearance of their tumor, known as a complete response, compared with 24 of the 180 patients in the CROSS group.

Patients who received the FLOT regimen lived a median of 5 years and 6 months, compared with about 3 years for patients in the CROSS group. Three years after completion of treatment, 57% of people in the FLOT group and 51% of patients in the CROSS group were still alive.

The rate of complications after surgery was similar among both groups. However, within 90 days of surgery, about 3% of participants in the FLOT group had died, compared with nearly 6% of participants in the CROSS group.

Considering the role of immunotherapy

The FLOT regimen should now be the standard of care for most people with locally advanced esophageal cancer, Dr. Goodman agreed.

But with the rise of immunotherapies, that may change.

For example, a trial called CheckMate 577 showed that giving the immunotherapy drug nivolumab (Opdivo) after the CROSS regimen and surgery may be an effective option.

In that trial, which included people considered to be at high risk of their cancer coming back, giving nivolumab after surgery improved how long participants lived without their disease returning.

So particularly in combination with nivolumab, CROSS may have some advantages for certain patients, Dr. Goodman pointed out.

For example, people with esophageal cancer tend to be elderly and have other health problems, she explained. “The CROSS regimen is … very well tolerated by these patients. And I think … the CROSS regimen, followed by adjuvant nivolumab, is still a potential option for many of these patients,” Dr. Goodman said.

Other studies are also testing the addition of immunotherapies, including other immune checkpoint inhibitors, into existing treatment regimens for locally advanced esophageal cancer. And still other studies are evaluating the combination of FLOT and CROSS.

“Given the poor prognosis with this disease, we need to continue to develop clinical trials [involving] novel treatment combinations and select patients who will respond best to specific treatments,” Dr. Goodman said.

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